SYNTHESIS OF POLYMETHOXYQUERCETIN MANNICH BASE DERIVATIVES AND THEIR ANTIPROLIFERATIVE ACTIVITY ON HUMAN CANCER CELL LINE

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Abstract. Several novel of polymethoxyquercetin Mannich base derivatives (2-7) were synthesized through *O*-methylation and based on Mannich reaction with various secondary amines and formaldehyde, starting from abundant and inexpensive natural sources quercetin. All the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR and MS techniques and the synthetic compounds were test for antiproliferative activities on human cervical carcinoma Hela cell line by the standard CCK-8 assay, the result showed that most of the target compounds exhibited moderate to potent antiproliferative activities on Hela (cervical carcinoma) cell which is comparable to the positive control *cis*-Platin. Among them, polymethoxyquercetin Mannich base derivatives (**2)** showed the strongest activity (IC_{50} 3.80 μM), they are potential and selective anticancer agent and worthy of further development.

Keywords. Quercetin; Polymethoxyquercetin; Mannich base derivatives; Synthesis; Cytotoxic activity

1. INTRODUCTION

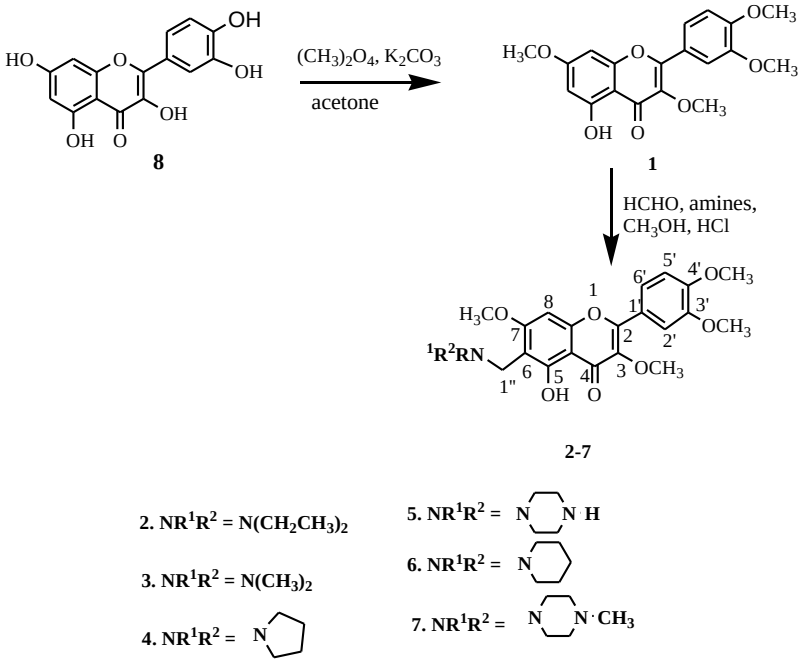
Polymethoxyflavonoids (PMFs) are a class of natural products, which almost exclusively exist in Citrus species, particularly in the peel of sweet orange [*Citrus sinensis* (*L.) Osbeck*] and mandarin (*Citrus reticulata* Blanco) [1]. Recently, quite a few studies focused on the PMFs in Citrus plants because they were found to possess distinguished anticarcinogenic, anti-inflammatory and antiviral activities [2-4].

Over the past decade, many biological studies have focused on two of the most abundant PMFs in Citrus peels: tangeretin and nobiletin. For example, tangeretin (5,6,7,8,4'-pentamethoxyflavone) was demonstrated to be an antiproliferative agent against a variety of tumor types [5], to induce G_1 cell-cycle arrest in human colorectal carcinoma and induce colon cancer cells apoptosis [6], it was identified as an effective multidrug resistance modulator[7]. Nobiletin (5,6,7,8,3',4'-hexamethoxyflavone), another abundant PMFs in Citrus peel, has been reported to exhibit antiproliferative activity on HL-60 cell line[8], to inhibit tyrosinase activity and to exhibit antimutagenic activity[9]. In particular, increasing attention has been paid to its antitumor metastatic activity due to the inhibition of gene expression and production of some matrix metalloproteinases (MMP-1,-3 and -9) [10].

PMFs generally present as minor components in the Citrus plants. The synthesis of these compounds have been much less studied, the full potential of this group to be used as drugs or bioactive molecules has not been realized. Recently we has reported the total synthesis of some polymethoxyflavonoids such as nobiletin, tangeretin and so on, as a continuation of our investigation of bioactive flavonoids and development of new antitumor activity compounds [11,12]. In this paper, we reported the new synthesis of a series of Citrus polymethoxyflavonoids. Furthermore, all synthesized compounds were evaluated for their antiproliferative activity on human cervical carcinoma Hela cell by the standard CCK-8 assay. The summary of the synthetic pathway adopted was illustrated in **Scheme 1**.

It has recently become more apparent that most of the important classes of drugs, especially those derived from natural products are nitrogen-containing compounds [13]. The Mannich reaction is a versatile reaction that leads to the incorporation of amines into organic molecules [14]. The presence of amine moiety in many natural products may increase biological potency due to the greater number of molecular sites for electrophilic attack by cellular constituents, as well as due to the cascade effect of preferential

chemosensitization. Amine moiety in drugs also could enhance physicochemical properties (*e.g*, water solubility) and improve bioavailability of bioactive molecules [15].



Scheme 1: **Synthesis of polymethoxyquercetin** Mannich base **derivatives**

2. RESULT AND DISCUSSION

Synthetic pathway was adopted to synthesize the Mannich base of polymethoxyquercetin as illustrated in Scheme 1. Synthesis of polymethoxyquercetin (1) originated from quercetin and anhydrous K_2CO_3 in acetone was stirred for 30 minutes at room temperature, then $(CH_3)_2SO_4$ was slowly added by dripping, the product was separated by chromatography column for 80% yield.

Mannich is synthesized by derivatives of different phenols and is widely used in the formation of amino alkyl chains [16-18]. Mannich derivatives of compounds are synthesized by the reaction of polymethoxyquercetin with different secondary amines such as: diethylamine, dimethylaniline, 1-methylpiperazine, pyrrolidine, 4-methylpiperidine, piperidine and formaldehyde. The classical conditions of the Mannich reaction to the phenolic compounds obtained are based on the substrate, the amine and the proportion of formaldehyde in the wine with extended heating [19-23]. In our case, polymethoxyquercetin, formaldehyde and secondary amines in the ratio 1: 1.2: 1.2 and stirred at 70 °C for 1-3 hours. We have aminomethylated at position C-6 of polymethoxyquercetin to produce 2-7.

This work began with the hypothesis that introducing nitrogen into a flavonoid molecule would improve the biological activity of the molecule. We have therefore initiated this study with the synthesis of a series of nitrogen-containing flavonoid derivatives by performing the Mannich reaction to polymethoxyquercetin. Mannich reaction requires a working hydrogen atom. This reaction can therefore be applied to the aromatic rings providing a flexible hydroxyl group available at the ortho position at C6.

For the polymethoxyquercetin (**1**) in the IR spectrum, the characteristic peaks of the OH-Ar group at appear 3349 cm^{-1}, the peaks at 2917 and 2840 cm^{-1} represent for the characteristic of the CH groups of the aromatic nucleus, peak at 1649 cm^{-1} and 1610 cm^{-1} represent the C=O group, while peak represents for the CO group at appear 1255, 1225 cm^{-1} and peak at 829 and 627 cm^{-1} represents the OCH_3 group. In the ^{1}H-NMR spectrum, specific OCH_3 groups were found at δ 3.97 (s, 6H), 3.88 (s, 3H), 3.86 (s, 3H), signal at 12.65 ppm is a signal of chelated OH at C-5 of **1**. In the ^{13}C-NMR spectrum of compound 1, the characteristic signals at the peak δ 178.4 (C = O), the peak at δ 96.2 (C-8), the peak at δ 92.3 (C-6) and the peak of carbon atoms of OCH_3 groups the peak at δ 60.3 (C7-OCH_3), 56.2 (C4 'and C3'-2OCH_3) and

the peak at δ 55.5 (C-OCH_3). In MS-ESI m/z the maximum the peak at 359 is an ion $[M+H]^+$ with a molecular weight consistent with compound 1.

The Mannich reaction has been synthesized by different phenol derivatives and was widely used in the introduction of basic aminoalkyl chain. [24,25] The Mannich base derivatives of the title compounds ware synthesized by reacting of (**1)** with different secondary amines (diethylamine, dimethylanilin, 1-methylpiperazine, pyrrolidine, 4-methylpiperidine, piperidine) and formaldehyde, regioselectively. The classical conditions of the Mannich reaction for the phenol compounds were based on the ratio of substrate, amines and formaldehyde in alcohol and heating time. [26] The orientation and by-products of the Mannich reation of phenols principally concerned were attack on the *o*-position. In our case, the polymethoxyquercetin, formaldehyde and secondary amines were in 1:1.2.1.2 ratio, respectively, and stirred at reflux for 1–3 hour. We are able to regioselectively synthesize C-6 aminomethylated of polymethoxyquercetin (2-7), respectively.

The structures of the polymethoxyquercetin Mannich base derivatives (**2-7**) were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra analysis. In FT-IR spectra, peak at 3326 cm^{-1} for the center of the OH group were linked to the aromatic nucleus, peak at 2931 cm^{-1} the base of the CH group in the aromatic nucleus, peak at 1658 cm^{-1} for the base of the C=O group, peak at 1255 cm^{-1} is typical for the C=O, peak at 1030-2030 cm^{-1} for the NH group. The ^{1}H-NMR spectrum of **2-7** indicates the absence of the signal at δ 6.36 for the H-6 proton of the polymethoxyquercetin **1**. Within loop A, the signals at δ 3.68-3.87 indicate the presence of a methyl amino group on the polymethoxyquercetin.

All synthesized compounds were evaluated for their cytotoxic potential against human cancer cell line Hela by the standard CCK8 method. The results were shown in **Table 1**. Overall, the majority of these Mannich base compounds displayed higher (lower IC_{50} values) cytotoxic activities than the positive control drug *cis*-Platin. Some compounds possess the IC_{50} value below 10 μM.

Table 1 Half-inhibitory concentration [IC50 (μM)] of compound 1-7 on human cancer cell line Hela

Compound	Hela	Compound	Hela
1	14.95	**6**	6.57
2	3.80	**7**	8.61
3	9.41	8	81.70
4	16.90	*cis*-Platin[a]	41.25
5	5.67	Paclitaxel[a]	0.040

[a]*cis*-Platin and Paclitaxel were employed as positive control.

3. EXPERIMENTAL

3.1 General methods

Melting points were measured on a XRC-I apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 instrument, using tetramethylsilane as an internal standard chemical shifts (δ) in ppm, and coupling constants (J) in Hz. Mass spectra (MS) or high-resolution mass spectrometry (HRMS) was determined with VG Autospec-3000 or Mat 95 XP spectrometer by the EI or ESI method (at the Hunan University China). Infrared spectra were recorded with KBr on Shimadzu 4700 typeA spectrophotometer at Industrial University of Ho Chi Minh City. Column chromatography was carried out on silica gel using 200–300 mesh. Quercetin was supplied by Sigma-Aldrich Company with purity over 99%. Commercially available AR or chemical pure reagents, and anhydrous solvent removed water and redistilled were employed. Biological activity was tested at the biology Institute of Hunan University of China.

3.1.1. Synthesis of 5-hydroxy-3,7,3',4'-tetramethoxyflavone (polymethoxyquercetin, 1)

The solution of quercetin (5 g, 15.15 mmol) and dry K_2CO_3 (4.5 g, 65.16 mmol) in 200 mL acetone was stirred for 30 mins at room temperature, then $(CH_3)_2SO_4$ (5 mL, 52.75 mmol) was slowly added dropwise. The mixture was stirred for 4 hours at 25 °C. Then the organic phase was separated. the solid thus obtained was purified by column chromatography over silica gel (petroleum ether /EtOAc, *v/v*, 10:1) to give **1** (5 g, Yield: 80%) yellow crystals, m.p. 115-117 ^oC; IR (KBr) ν_{max} cm^{-1}: 3349, 2917, 2840, 1649, 1610, 1255, 829, 627; ^1H NMR (400 MHz, $CDCl_3$): δ *(ppm)* 12.65 (s, 1H, 5-OH), 7.74 (d, *J* = 8.5, Hz, 1H, H-6'), 7.69 (s, 1H, H-2'), 7.00 (d, *J* = 8.5 Hz, 1H, H-5'), 6.45 (d, *J* = 2.1 Hz, 1H, H-8), 6.36 (d, *J* = 2.1 Hz, 1H, H-6), 3.97 (s, 6H, 4'-OCH_3 and 5'-OCH_3), 3.88 (s, 3H, 7-OCH_3), 3.86 (s, 3H, 3-OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4 (C=O), 166.9 (C-7), 161.4 (C-5), 158.0 (C-8a), 157.7 (C-2), 149.2 (C-3'), 148.8 (C-4'), 139.4 (C-3), 122.8 (C-1'), 121.4 (C-6'), 111.7 (C-5), 111.1 (C-2'), 105.1 (C-4a), 96.2 (C-8), 92.3 (C-6), 60.3 (C7-O$\underline{C}H_3$), 56.2 (C4' and C3'-2O$\underline{C}H_3$), 55.5 (C-OCH_3); MS m/z (ESI): 359 $[M+H]^+$.

3.1.2. General experimental procedure for Mannich base derivatives (2-7)

The mixture of 37% formaldehyde (aq, 4.11 mL, 0.50 mmol) and secondary amine (0.50 mmol) in 10 mL of methanol and 0.02 mL of 15% HCl(aq) were stirred at 70 ^oC untill the complete homogenization. The solution obtained was added slowly to a solution of polymethoxyquercetin (150 mg, 0.42 mmol) in methanol, and the reaction mixture was refluxed for 1–3 h. The solvent was removed under reduced pressure and the residue diluting with H_2O, the solution was extracted by EtOAc (3×30 mL), the extracts were combined and the solvent was removed under reduced pressure, dried over anhydrous Na_2SO_4, the crude solid was recrystallized with EtOAc/ petroleum ether to afford **2-7** as yellow crystals in 76–93% yields.

3.1.3. Synthesis of 5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-6-((diethylamino)methyl)--4H-chromen-4-one (2)

Yield: 76%; yellow crystals, m.p. 119-121 ^oC; IR (KBr) ν_{max} cm^{-1}: 3326, 2931, 2840, 1658, 1610, 1255, 829, 627; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.4 Hz, 1H, H-6'), 7.38 (s, 1H, H-2'), 6.83 (d, *J* = 8.4 Hz, 1H, H-5'), 6.24 (s, 1H, H-8), 3.96 (s, 3H, 7-OCH_3), 3.81 (s, 6H, 3'-OCH_3 and 4'-OCH_3), 3.77 (s, 3H, 3-OCH_3), 3.69 (s, 2H, 2H, 1''-CH_2), 2.67 (q, *J* = 7.2 Hz, 4H, 2CH_2), 1.0 (t, *J* = 7.2 Hz, 6H, 2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3 (C=O), 158.0 (C-7), 157.3 (C-5), 155.8 (C-8a), 154.9 (C-2), 149.1 (C-4') 148.8 (C-3'), 139.3 (C-3), 130.6 (C-6), 122.7 (C-1'), 121.4 (C-6'), 111.5 (C-5'), 111.4 (C-2'), , 97.1 (C-8), 60.3 (C-OCH_3), 56.1 (C3' and C4'-2O$\underline{C}H_3$), 55.8 (C-OCH_3), 53.6 (2C-$\underline{C}H_2$), 46.7 (C1''-CH_2), 11.6 (2C-CH_3); MS m/z (EI): 444 $(M)^+$

3.1.4. Synthesis of 5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-6-((dimethylamino)methyl)--4H-chromen-4-one (3)

Yield: 79%, yellow crystals, m.p. 113-115 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.4 Hz, 1H, H-6'), 7.39 (s, 1H, H-2'), 6.83 (d, *J* = 8.4 Hz, 1H, H-5'), 6.24 (s, 1H, H-8), 3.95 (s, 3H, 3'-OCH_3), 3.82 (s, 3H, 4'-OCH_3), 3.81 (s, 3H, 7-O$\underline{C}H_3$), 3,77 (s, 3H, 3-O$\underline{C}H_3$), 3.68 (s, 2H, 6-$\underline{C}H_2$N), 2.42 (s, 6H, 2$\underline{C}H_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4 (C=O), 158.0 (C-5), 157.4 (C-7), 155.8 (C-4a), 154.9 (C-2), 149.2 (C-4'), 148.8 (C-3'), 139.4 (C-3), 130.7 (C-6), 122.8 (C-1'), 121.5 (C-6'), 111.5 (C-5'), 111.1 (C-2'), , 105.7 (C-8a), 97.2 (C-8), 60.0 (C-OCH_3), 56.2 (C3' and C4'-2O$\underline{C}H_3$), 55.9 (C-OCH_3), 53.7 (C-2CH_3), 45.1 (C1''-$\underline{C}H_2$N); MS m/z (EI): 416 $(M)^+$.

3.1.5. Synthesis of 5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-6-((pyrrolidin-1-yl)methyl)-4H-chromen-4-one (4)

Yield: 81%, yellow crystals, m.p. 189-190 ^oC; IR (KBr) ν_{max} cm^{-1}: 3397, 2920, 2846, 1661, 1620, 1421, 1258, 829, 588; ^1H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ 7.69 (d, *J* = 8.4 Hz, 1H, H-6'), 7.38 (s, 1H, H-2'), 6.83 (d, *J* = 8.4 Hz,1H, H-5'), 6.25 (s, 1H, H-8), 3.96 (s, 3H, 4'-OCH_3), 3.84 (s, 2H, 6-CH_2N), 3.82 (s, 3H, 3'-OCH_3), 3.81(s, 3H, 7-OCH_3) 3.77 (3H, 3-OCH_3), 3.02 (m, 4H, 2CH_2), 1.98 (m, 4H, 2CH_2); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 178.4 (C=O), 158.0 (C-5), 157.4 (C-7), 155.8 (C-4a), 154.9 (C-2), 149.3 (C-4'), 148.8 (C-3'), 139.4 (C-3), 130.7 (C-6), 122.7 (C-1'), 121.5 (C-6'), 111.5 (C-5'), 111.1 (C-2'), 105.7 (C-8a), 97.2 (C-8), 60.4 (C-OCH_3), 56.2 (2C-2OCH_3), 55.9 (C-OCH_3), 53.8 (2C-CHN), 53.7 (C1''-CH_2N), 23.5 (2C-2CH_2); MS m/z (EI): 442 $(M)^+$.

3.1.6. Synthesis of 5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-6-((piperidin-1-yl)methyl)-4H-chromen-4-one (5)

Yield: 78%, yellow crystals, m.p. 220-221 ^oC; IR (KBr) ν_{max} cm^{-1}: 3371, 2920, 2850, 1649, 1604, 1255, 832, 627; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.4 Hz, 1H, H-6'), 7.38 (s, 1H, H-2'), 6.83 (d, J = 8.4 Hz, 1H, H-5'), 6.25 (s, 1H, H-8), 3.96 (s, 3H, 3'-OCH_3), 3,87 (s, 2H, 6-CH_2N), 3.82 (4'-OCH_3) 3.81 (7-OCH_3), 3.77 (s, 3H, 3-OCH_3), 2.73 (q, J= 7.2 Hz, 4H, 2CH_2), 2.54 (m, 4H, 2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.1 (C=O), 158.0 (C-5), 157.4 (C-7), 155.8 (C-8a), 154.9 (C-1), 149.2 (C-4'), 148.8 (C-3'), 139.4 (C-3), 130.7 (C-6), 122.8 (C-1'), 111.5 (C-6'), 111.4 (C-5'), 111.1 (C-2'), 105.6 (C-4a), 97.2 (C-8), 60.4 (C-OCH_3), 56.1 (2C-2OCH_3), 55.9 (C-OCH_3), 54.5 (C-2$\underline{C}H_2$N), 53.7 (2C-2$\underline{C}H_2$NH); 44.8 (C1''-CH_2); MS m/z (EI): 457 $(M)^+$.

3.1.7. Synthesis of 5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-6-((piperidin-1-yl)methyl)-4H-chromen-4-one (6)

Yield: 86%, yellow crystals, m.p. 189-191 oC; IR (KBr) ν_{max} cm^{-1}: 3388, 2917, 2846, 1655, 1626, 1543, 1424, 1357, 1264, 829, 588; ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 8.4 Hz, 1H, H-6'), 7.38 (s, 1H, H-2'), 6.83 (d, J = 8.4 Hz, 1H, H-5'), 6.25 (s, 1H, H-8), 3.96 (s, 3H, 3'-OCH_3), 3.85 (s, 2H, CH_2N), 3.82 (s, 3H, 4'-OCH_3), 3.81 (s, 3H, 7-OCH_3), 3.77 (s, 3H, 3-OCH_3), 2.58 (m, 4H, 2CH_2), 1.73 (m, 4H, 2CH_2), 1.47 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4 (C=O), 158.0 (C-5), 157.4 (C-7), 155.8 (C-8a), 154.9 (C-1), 149.2 (C-4'), 148.8 (C-3'), 139.4 (C-3), 130.7 (C-6), 122.8 (C-1'), 121.5 (C-6'), 111.5 (C-5'), 111.1 (C-2'), 105.7 (C-4a), 97.2 (C-8), 60.4 (C-OCH_3), 56.2 (2C-2OCH_3), 55.9(C-OCH_3), 53.7 (C1''-CH_2), 53.5 (C-2$\underline{C}H_2$N), 26.3.0 (2C-2CH_2), 24.1 (C-CH_2); MS m/z (EI): 456 $(M)^+$.

3.1.8. Synthesis of 5-hydroxy-3,7-dimethoxy-2-(3,4-dimethoxyphenyl)-6-((4-methylpiperazin-1-yl)methyl)-4H-chromen-4-one (7)

Yield: 93%, yellow crystals, m.p. 210-211 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.4 Hz, 1H, H-6'), 7.38 (s, 1H, H-2'), 6.83 (d, J = 8.4 Hz, 1H, H-5'), 6.25 (s, 1H, H-8), 3.96 (s, 6H, 3'-OCH_3), 3.87 (s, 2H, 6-CH_2N), 3.82 (s, 3H, 4'-OCH_3), 3.81 (s, 3H, 7-OCH_3), 3.77 (s, 3H, 3-OCH_3), 2.62 (m, 4H, 2CH_2), 2.53 (m, 4H, 2CH_2), 2.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4 (C=O), 158.0 (C-5), 157.4 (C-7), 155.8 (C-8a), 154.9 (C-1), 149.2 (C-3'), 148.1 (C-4'), 139.4 (C-3), 130.7 (C-6), 122.7 (C-1'), 121.4 (C-6'), 111.5 (C-5'), 111.1(C-2'), 105.6 (C-4a), 97.3 (C-8), 60.4 (C-OCH_3), 56.2 (2C-2OCH_3), 55.9(C-OCH_3), 54.6 (2C-2$\underline{C}H_2$N), 53.7 (C-2CH_2), 53.0 (C1''-CH_2), 46.0 (C-CH_3); MS m/z (EI): 470 $(M)^+$.

3.12 Assay for antiproliferative activity

The antiproliferative activity was tested using a CCK-8 assay on Human cervix carcinoma cell line (Hela). Briefly, cells (5 x 10^3 per well in a 96-well plate) were treated with different concentrations of compounds **1-8** (100, 25, 6.25, 1.56, 0.39, 0.0976, 0.0244, 0.0061 µM) for 48 h. Then 5% CCK-8-solution was added into each well and incubated with 90% humidity and 5% CO_2 for another 1-3 h. Color development was quantified photometrically at 450 nm, and used an EL x 808 (Bio-Rad 680) Absorbance Microplate Reader to determine the concentration that killed 50% of cells (IC_{50}). To stop the color reaction by add 10 µL of 1 % Sodium dodecyl sulfate (SDS) [(dissolve 0.1 g SDS with phosphate buffer saline (PBS) buffer to prepare 10 mL solution)] or add 10 µL of 0.1 mol/L acid such as hydrochloric acid.

4. CONCLUSION

In summary, we succeeded in developing a new synthetic route for polymethoxyflavonoids (**1**) from commercially low-cost quercetin, and synthesis of a novel series of polymethoxyquercetin Mannich base derivatives with various secondary amines and formaldehyde, six new flavonoid Mannich base

derivatives **2-7** were synthesized. Furthermore, all the synthetic compounds were tested for antiproliferative activity against a panel of human cancer cell lines including Hela. The antiproliferative activity test demonstrated that compounds **2, 5, 6, 7, 3** were more potent (lower IC_{50} values) against Hela cells with IC_{50} values of 3.80-9.41 μM than the positive control *cis*-Platin (IC_{50} 41.25 μM). The results indicated that these compounds are potential anticancer agents and are promising for further development.

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TỔNG HỢP CÁC DẪN XUẤT BAZƠ CỦA POLYMETHOXYQUERCETIN TRÊN CƠ SỞ PHẢN ỨNG MANNICH VÀ HOẠT TÍNH ỨC CHẾ TĂNG SINH TRÊN DÒNG TẾ BÀO UNG THƯ Ở NGƯỜI

Tóm tắt. Các dẫn xuất mới của polymethoxyquercetin (**2-7**) trên cơ sở phản ứng Mannich đã được tổng hợp thông qua quá trình methyl hóa và dựa trên phản ứng Mannich với các amine bậc hai khác nhau và formaldehyd, bắt đầu từ nguồn quercetin tự nhiên dồi dào và rẻ tiền. Tất cả các hợp chất tổng hợp đã được xá nhận cấu trúc bằng các phương pháp hóa lý như: ^{1}H NMR, ^{13}C NMR và MS và các hợp chất tổng hợp đã được thử nghiệm ức chế tăng sinh trên dòng tế bào ung thư cổ tử cung Hela bằng phương pháp CCK-8 tiêu chuẩn, kết quả cho thấy hầu hết các hợp chất thể hiện ở mức độ vừa phải và tốt ức chế tăng sinh trên dòng tế bào ung thư Hela ở người, các kết quả đã được so sánh với *cis*-Platin là chất đối chứng dương. Trong số đó, dẫn xuất polymethoxyquercetin Mannich (**2**) thể hiện hoạt tính mạnh nhất (IC_{50} 3,80 μM.

Từ khóa. quercetin; polymethoxyquercetin; dẫn xuất Mannich bazơ; tổng hợp; ức chế tăng sinh

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